REMARKS

Formal Matters

Claims 1, 4, and 6-12 are now pending in this application. Applicants thank the Examiner for withdrawing the provisional obviousness-type double patenting rejection of claims 1-8, the 35 U.S.C. § 112, second paragraph rejection of claim 1, and the rejection of claim 6 under 35 U.S.C. § 112, first paragraph. Applicants have amended claims 1, 4, 6, and 7, and added new claims 9-12. Support for these amendments may be found in the specification at least the following locations:

Claim	Support
1	page 2, line 3; original claim 5; page 7, line 1
4	page 17, lines 1-2
6	typographical correction and change in dependency
7	change in dependency
9	page 2, lines 4-5
10	page 18, lines 12-16; page 22, lines 11-19
11	page 18, line 13; page 22, line 17
12	page 17, line 3

New Anticipation Rejections

The Examiner rejected claims 1, 2, and 8 as being anticipated by both Rosen et al. (Calcified Tissue International 61:455-459, 1997) and WO 92/00753. The Examiner further asserted that both Rosen et al. and WO 92/00753 teach a method that comprises administering to a patient a polypeptide agonist or antagonist that is capable

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of inhibiting the binding of PTHrP to a receptor thereof. Claims 1-5 and 7-8 were also rejected by the Examiner as being anticipated by Yoneda et al. (U.S. Patent 5,626,845). Yoneda et al. teach a monoclonal antibody directed against PTHrP and mention that this antibody may be humanized.

Applicants traverse this rejection. First, none of the references teach a method for treating **hypercalcemic crisis**. The references discuss treatment of simple hypercalcemia. In contrast, hypercalcemic crisis is characterized by more serious symptomology, such as impaired consciousness (due to factors such as cardiac arrest and/or coma) and these aspects are now clearly recited in the claims. Applicants have also added the limitation "decreasing a blood calcium level that is above 10.4 mg/dl to effectively treat the patient" to further distinguish between the two conditions. Thus, the prior art does not teach the presently claimed method.

Additionally, none of these three references describe a specific humanized antibody. Applicants invention is directed to humanized antibodies and Applicants have amended claim 1 to clarify this aspect of the invention. Applicants have cancelled claims 2, 3, and 5, as they would have been duplicative of amended claim 1. It is widely recognized that it is extremely difficult to produce a humanized antibody that retains the binding properties and functional activity of an original murine or chimeric antibody. Thus, the mere mention of humanizing antibodies in Yoneda et al. is not sufficient to enable the preparation of humanized antibodies and is therefore not anticipating.

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Obviousness Rejection

The Examiner maintained the rejection of claims 1-8, under 35 U.S.C. § 103(a), as allegedly being obvious over Sato et al. (Journal of Bone and Mineral Research, 8/7:849-60 (1993)) in view of Yoneda et al. (U.S. Patent 5,626,845).

The Examiner did not find Applicants previous arguments regarding the difference between hypercalcemia and hypercalcemic crisis convincing. The Examiner stated that "both conditions share at least one symptom that is expected to be ameliorated upon administering the substance to a patient." Office Action at page 10.

First, Applicants wish to emphasize the differences between hypercalcemia and hypercalcemic crisis. The main differences between the two conditions are the very rapid rise in calcium levels in hypercalcemic crisis and the more serious symptomology that accompanies it, especially impaired consciousness. Applicants have amended the claims to indicate the more serious symptomology of hypercalcemic crisis by reciting that the this condition is associated with impaired consciousness.

Applicants have also amended the claim to add the limitation that the patient has a blood calcium level above 10.4 mg/dl prior to treatment to further distinguish between the two conditions in the claims. Further, Applicants note the failure of typical hypercalcemia treatments, such as calcitonin and bisphosphonate, to treat hypercalcemic crisis. Specification, page 3, lines 13-23. This suggests that there are different physiological mechanisms underlying the two disorders.

Finally, Applicants address the Examiner's argument that "both conditions share at least one symptom that is expected to be ameliorated upon administering the

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substance to a patient." Applicants have deleted the phrase "at least one symptom of" from claim 1 and listed the various symptoms associated only with hypercalcemic crisis (not simple hypercalcemia) to be treated by the present invention in claim 9. Applicants assert that this obviates the Examiner's rejection of claim 1 and the other claims that are dependent on claim 1.

Indefiniteness Rejection

The rejection of claim 4 for indefiniteness was maintained by the Examiner, despite Applicants previous argument that the terms "fragment" and "modified" are defined in the specification as they relate to the use of antibodies. Further, the Examiner stated "although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims."

In addition to interpreting the claim in light of the specification, claim language must also be analyzed by the teachings of the prior art and as one of ordinary skill in the art would understand the claim. The term antibody "fragment" is understood with a reasonable degree of clarity by one of ordinary skill in the art to mean a portion of an antibody that retains binding specificity for a particular antigen. In addition, teachings of the prior art define different parts of an antibody, such as Fab and scFv that conform to this definition. Indeed, the specification recites at page 17, lines 1-2 that an antibody within the scope of the invention encompasses any fragment or modified product of a fragment that can "bind to PTHrP and inhibit the activity of the PTHrP." Finally, Applicants add dependent claim 12 to more clearly describe these particular fragments.

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Nevertheless, to address the alleged indefiniteness of the term "modified," Applicants have removed this limitation from claim 4 and added new claims 10 and 11 to better describe the invention. New claims 10 and 11 are supported in the specification on page 22, lines 13-19.

The Examiner rejected claim 4 as allegedly being indefinite by using the limitation "wherein the substance is at least one of a fragment of an anti-PTHrP antibody or a modified form of the fragment." Office Action at page 8. The Examiner suggests that if Applicants replace the "or" with "and," the claim would be proper. This rejection is moot as Applicants have amended claim 4 for other reasons.

The Examiner rejected claims 1-8 under 35 U.S.C. §112, second paragraph because "the former claims were drawn to a therapeutic agent comprising a substance that is capable of inhibiting the binding of PTHrP to a receptor thereof, while the present claims are drawn to a method comprising administering to a patient a substance capable of inhibiting the binding of PTHrP to a receptor thereof." As MPEP §2172 states, "(t)he second paragraph of 35 U.S.C. 112 does not prohibit applicants from changing what they regard as their invention during the pendency of the application."

New Written Description Rejection

The Examiner made a new written description rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph. The Examiner stated that "the specification does not describe the production of a substance that is capable of preventing a symptom of a hypercalcemic crisis; furthermore, the specification does not describe the use of such a

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substance to prevent a symptom of a hypercalcemic crisis." Applicants have amended claim 1 to delete the objected-to word "preventing" merely to facilitate prosecution, although Applicants believe this concept is supported in the specification. Applicants request that the Examiner withdraw this rejection.

New Enablement Rejection

The Examiner made a new enablement rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph. The Examiner stated that:

> the teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification set forth therein is insufficient to enable the skilled artisan to have a reasonable expectation of successfully using the claimed invention to prevent or treat a symptom of hypercalcemia or an acute crisis thereof without having the need to perform additional, undue experimentation.

Office Action at page 5.

Applicants point the Examiner to Reference Examples 1-5, which clearly outline the process of making humanized PTHrP antibodies and confirmation of their functional activity. The skilled artisan is also enabled to use the claimed invention, as use of a humanized PTHrP antibody to treat hypercalcemic model rats is described in Example 2 and Figures 1-6. Animal models are acceptable evidence of enablement. Further, means of administration of the antibody and dosages are described in the specification at page 21, line 20 to page 23, line 5. Thus, one of ordinary skill in the art based on these teaching would be able to both make and use the humanized antibodies of the

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invention. In light of the amendment to claim 1, and these arguments, Applicants request that the Examiner withdraw this rejection.

The Examiner rejected claims 1-8 under 35 U.S.C. § 112, first paragraph, for containing the following phrases:

- "method for preventing or treating at least one symptom of hypercalcemic crisis;"
- "administering to a patient at least one substance;" and
- "wherein said substance is at least one of a fragment . . . or a modified form of the fragment"

because "there does not appear to be proper and sufficient antecedent basis in the specification for recitation of this claim language." Office Action at page 7. The Examiner also stated that "recitation of such claim language appears to introduce new matter." Specifically, Applicants believe that the Examiner is objecting to the term "at least one" in all of the quoted phrases.

There is no requirement that the words in the claim must match those used in the specification disclosure. As MPEP §2163(I)(B) "While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." Applicants believe that this claim language is supported in the specification, but in order to advance prosecution, have removed the term "at least one" from the claims. Thus, Applicants request that the Examiner withdraw this rejection.

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Conclusion

Applicant respectfully requests that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing the claims in condition for allowance. Applicants submits that the proposed amendments of the claims do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

Furthermore, Applicants respectfully point out that the final action by the Examiner presented some new arguments as to the application of the art against Applicant's invention. It is respectfully submitted that the entering of the Amendment would allow the Applicants to reply to the final rejections and place the application in condition for allowance.

Finally, Applicants submit that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

In view of the foregoing remarks, Applicants submit that this claimed invention, as amended, is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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APPENDIX TO THE AMENDMENT

1. (Twice Amended) A method for ~~preventing or~~ treating ~~at least one symptom of~~ a patient suffering from or susceptible to hypercalcemic crisis associated with impaired consciousness, comprising

~~the step of~~ administering to a patient ~~at least one substance~~ a humanized anti-PHTrP antibody capable of inhibiting the binding between PTHrP and a receptor thereof and

allowing the antibody to inhibit the binding of PTHrP to a receptor thereof; wherein the patient has a blood calcium level above 10.4 mg/dl prior to treatment.

4. (Twice Amended) The method according to claim 1, wherein the ~~substance is at least one of a fragment of an~~ humanized anti-PTHrP antibody ~~or a modified form of the fragment~~ is an antibody fragment capable of inhibiting the binding between PTHrP and a receptor thereof.

6. (Twice Amended) The m~~M~~ethod according to claim 1~~5~~, wherein the humanized antibody is humanized #23-57-137-1 antibody.

7. (Twice Amended) The method according to claim 1~~3~~ or 4, wherein the antibody is a monoclonal antibody.

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